

Remarks

Applicants acknowledge, with thanks, the withdrawal of the previous rejections under 35 USC §112, second paragraph and 35 USC §102.

No claim amendments are submitted at this time.

Rejections under 35 USC §103

The previously-issued rejection of claims 1 and 3-5 as being obvious over the combination of the documents Pende et al, 1999 and Mandelboim et al, 2001 is maintained.

The Examiner takes the position that on the one hand, it is not germane whether or not Mandelboim et al fails to teach lysis of cancer cells by NKp46D2-Ig and NKp30-Ig conjugates via a macrophage dependent mechanism not involving NK cells, "because the claims are composition claims and **not method claims**", and on the other hand, asserts that the NKp30-Fc conjugate of the subject application is obvious over Mandelboim et al and Pende et al in view of the teachings of those references regarding lysis of target cells by NK cells (pages 6-7 of the Office Action).

The Applicant respectfully submits that the Examiner is dismissive of the Applicant's previous arguments relating to NK receptor-mediated cell lysis on the basis that the claims are not directed to methods, and yet has invoked arguments based on the very same NK cell lysis activity to allege obviousness of the claimed conjugate.

The Applicant respectfully re-asserts that the combination of cited references does not render the claimed invention obvious.

Pende et al discloses that various monoclonal antibodies, including anti-CD16, anti-NKp46 and the anti-NKp30 antibody AZ20, enhance the cell killing activity of fresh NK cells against certain targets, and that the enhancement reportedly involves cross-linking of NKp30 (Fig 4A and p. 1509, 2nd column, 2nd paragraph). The same AZ20 antibody is disclosed to inhibit NK cell-mediated cytotoxicity against other cancerous targets, and the inhibition reportedly involves masking of NKp30 (Fig. 4B and p. 1510, 1st column), while an isotype-matched anti-CD56 antibody has no effect in any of the cell systems tested. No teaching is provided on how to distinguish between systems in which anti-NKp30 *cross-links* NKp30 versus those in which anti-NKp30 *masks* NKp30. Therefore, on the basis of Pende et al one of ordinary skill of the art would not be motivated to produce an NKp30-Ig conjugate on the basis of its ability to lyse cancer target cells with a reasonable expectation of success. The authors of Pende et al moreover raise the question of whether a correlation exists between ligand expression and susceptibility to NK-mediated lysis by different tumor cells (p. 1514, 2nd column, final sentence).

The deficiency of Pende et al is not remedied by Mandelboim et al. Mandelboim et al teaches that a direct interaction between NKp46 and haemagglutinin (HN) is involved in NK cell-mediated lysis, based on both binding experiments and cell lysis experiments. Fig 1a shows that the binding of the conjugate NKp46-Ig is increased in cells transfected with HN, as compared to non-transfected cells. Cell lysis is not measured in the experiment of Fig. 1a, despite the general legend of Figure 1. Figs. 1b and 1c show that antibody directed against the conjugate NKp46-Ig i.e. “anti-NKp46 serum” inhibits NK cell-mediated lysis of the HN-transfected target cells. Similarly, Fig. 2 shows that anti-NKp46 serum inhibits lysis of IV-infected cells. However, in the experiments depicted in Figs. 1b, 1c and 2, no NKp46-Ig conjugate is present, and thus contrary to the assertion of the Examiner, the inhibition is not directed against the interaction between NKp46-Ig conjugate and HN, but rather against the interaction between NKp46 (expressed on NK cells) and HN.

The Examiner asserts that the title, abstract and legend to Figure 1 indicate that Mandelboim et al conclude that recognition of HN on the target cells by NKp46 conjugate activates lysis. The Applicant asserts however, that one of ordinary skill in the art would understand from Mandelboim et al that NKp46 as expressed on cells, is involved in mediating cell lysis. Mandelboim et al provide no teaching or suggestion that the isolated conjugate NKp46-Ig has lytic activity. Accordingly, the title and the Abstract of the reference relate to recognition of HN by NKp46, NOT by NK-p46-Ig conjugate.

The Applicant moreover submits that Mandelboim et al actually teaches away from using the combination of an NK receptor, such as NKp46, and an antibody to effect lysis of target cells. More specifically, the experiments depicted in Figures 1b, 1c and 2 involve incubation of NK GAL cells (expressing NKp46) with anti-NKp46 serum (i.e. an antibody), yet that combination results in diminished lysis, thereby teaching away from the presently claimed invention.

The Applicant further respectfully traverses the Examiner's assertion that it would have been obvious to use the extracellular domain of NKp30 to make the NKp30-Fc conjugate, in view that the NKp46-Fc conjugate of Mandelboim et al uses the extracellular domain and in view that NKp30 belongs to the same Ig superfamily as NKp46. As is known by one of average skill in the art, the Ig superfamily comprises more than 200 related proteins having diverse functions, including for example antibodies, T cell receptor molecules, antigen presentation molecules, adhesion molecules, co-stimulatory molecules, and cytokine receptors. Many of these diversely functioning molecules are found on the same types of cells. Accordingly, the fact that NKp30 and NKp46 belong to the same superfamily does not render the conjugate fusion protein NKp30-Ig obvious over the prior art conjugate NKp46-Ig.

The Office Action further indicates that the previously-issued rejection of claims 19 and 21-23 as being obvious over the Pende et al, 1999 in view of Mandelboim et al, 2001 and further in view of Sukhatme et al (US 6,797,488) is maintained.

Sukhatme et al relates *inter alia* to use of a biologically active anti-angiogenic restin protein produced in a yeast expression system for treatment of malignant tumors.

The Applicant respectfully submits that one of ordinary skill in the art would not be motivated to combine either or both of Pende et al and Mandelboim et al with Sukhatme et al to arrive at the claimed pharmaceutical composition with a reasonable expectation of success.

More specifically, Pende et al and Mandelboim et al both utilize a mammalian expression system (COS-7 cells) to produce recombinant proteins of interest, whereas Sukhatme et al uses a yeast expression system. One of ordinary skill in the art is aware that mammalian and yeast expression systems can yield substantially different results following expression of any particular recombinant protein, particularly with respect to post-translational modifications, such as in the glycosylation pattern of the protein product. These differences can have significant impact on the means by which a protein product may be formulated into a pharmaceutical composition.

Furthermore, Sukhatme et al actually teaches away from a fusion protein comprising the Fc portion of an immunoglobulin, as disclosed and claimed in the present application, and as taught by Mandelboim et al. More specifically, Sukhatme et al teaches a fusion protein of endostatin and IgG “specifically with the Fc portion removed” (Sukhatme et al, column 2, lines 59-67).

Accordingly, the combination of the cited references does not render claims 19 and 21-23 obvious. For the above reasons, withdrawal of the rejections under 35 USC §103 is respectfully requested.

In view of the forgoing, the claims are believed in condition for allowance and such action is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative with any questions that arise in connection with the present application.

Respectfully submitted,

A handwritten signature in cursive script, reading "Kathy Smith Dias", is written over a horizontal line.

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